antidepressants, antipsychotics, anxiolytics, anti-migraine and sedatives." Furthermore, Claim 28 of the '699 application is not directed to method of treating depression by administering rotigotine. Rather, Claim 9 of the '699 application, from which Claim 28 depends, is a combination of (a) rotigotine or a metabolite, prodrug or physiologically acceptable salt thereof, (b) one or more additional active ingredients comprising one or more antidepressants, antipsychotics, sedatives, anxiolytics and/or anti-migraine agents. Claim 28 of the '699 application further recites wherein the one or more additional active ingredients comprise one or more antidepressants and a Markush group of antidepressants.

Furthermore, the rejection is provisional because the allegedly conflicting claims have not yet been patented. Applicant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the '699 application issues as a patent.

2. Non-statutory double patenting over Serial No. 11/060,997

Claims 17, 30, 37 and 51-55 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 5, 18, 23, 24, 27 and 28 of copending application Serial No. 11/060,997 (the '997 application).

Applicant again notes that Claim 17 is directed to a method of *treating depression* in a mammal by administering to the mammal a therapeutically effective amount of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol or a physiologically acceptable salt thereof. Whereas, for example, dependent Claim 18 of the '997 application, generally recites a method for treatment of dopaminergic neuron loss by (a) identifying a subject suffering from or susceptible to a disease associated with increased dopaminergic neuron loss; (b) administering rotigotine or a salt or prodrug thereof to the subject; and (c) wherein the subject additionally has one or more clinical symptoms including depression. The claimed method in the '997 application is not to treating depression. Furthermore, Claim 5 from the '997 application is cancelled.

Additionally, the '997 application claims priority to a continuation application of PCT/EP04/14655 dated 23 December 2004 and claims priority to a U.S. provisional application 60/546,611 dated 20 February 2004, which is later than the present application's priority date, *i.e.* 26 July 2003. See MPEP 804.I.B.1, first paragraph (emphasis added):

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Furthermore, the rejection is provisional because the allegedly conflicting claims have not yet been patented. Applicant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the '997 application issues as a patent.

3. Rejection under 35 U.S.C. §103(a) over the Alleged 3-Way Combination of Nichols in view of Pfeiffer and Lauterbach

Claims 17, 24-34, 37-55, and 78 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over an alleged combination of 3 documents: U.S. Patent No. 4,501,890 (Nichols) in view of Pfeiffer (2002), Drugs Aging, 19(8): 561-570 (Pfeiffer) and U.S. Patent Publication No. 2003/0027793 (Lauterbach). This 3-way rejection is respectfully traversed.

3.1. No Motivation To Combine the References

The Office Action (p. 7) provides the following as a motivation to combine the references:

> ...1) Nichols et al. provides the teaching that D2 agonist treat depression and Parkinson's disease; 2) Pfeiffer teaches that rotigotine is a known D2 agonist and well tolerated for transdermal Parkinson's disease in humans; [and] 3) Lauterbach teaches rotigotine in treating Parkinson's disease and further teaches that depression may also accompany Parkinson's disease.

Contrary to the Office Action's conclusions, the evidence of record establishes that one of ordinary skill in the art would not have been motivated to combine Nichols, Pfeiffer, and Lauterbach.

i. Evidence of D_2 Agonist Failure to Treat Depression (Although the D_2 Agonist Treats Parkinson's Disease).

Wang, *et. al* (2007) Chinese J. of Physiology 502(2): 63-68 (herein "Wang") reports on the effects of apomorphine (APO), an agonist for the D_1 and D_2 receptors, and supercede (SUL), a selective D_2 antagonist, on the expression of learned helplessness behavior. APO is

also known as a compound used in the treatment of Parkinson's disease. *See* http://en.wikipedia.org/wiki/Apomorphine (printed 5 May 2011).

However, the D_2 agonist used to treat Parkinson's disease, **APO, failed to treat depression**. Wang concluded that APO's "excessive stimulation of D_1 receptor may participate in the failure of coping behavior leading to learned helplessness and therefore in the pathophysiological mechanisms underlying the development of depression." Accordingly, the evidence of record exemplifies that a D_2 agonist and compound used in treating Parkinson's disease, like APO, can fail to treat depression, and for this reason alone, the Office Action's "motivation to combine" statement is insufficient to support a presumption of *prima facie* obviousness.

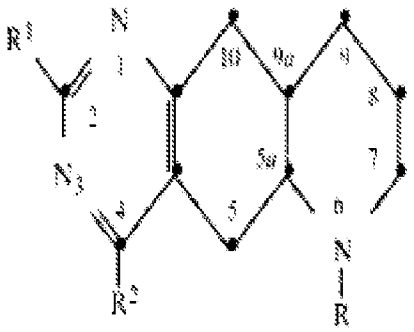
ii. Nichols' Compounds Are (1) Structurally Different and (2) Do Not Share the Same Receptor Profile or D_2 Agonist Activity as Rotigotine.

Rotigotine is structurally and chemically different than the compounds reported in Nichols. These numerous differences further distance any motivation to employ rotigotine to treat depression or combine Nichols with Pfeiffer and Lauterbach. Nichols states that the "compounds represented by Formulas III and IV are dopamine (D-2) agonists substantially devoid of other agonist or antagonist (blocking) activities." *See* col. 3, lines 20-23 (emphasis added). Contrary to the compounds reported in Nichols, rotigotine is not substantially devoid of other agonist or antagonist activity, and further rotigotine demonstrates a preference for the D_3 receptor not the D_2 receptor. Below is evidence of this fact.

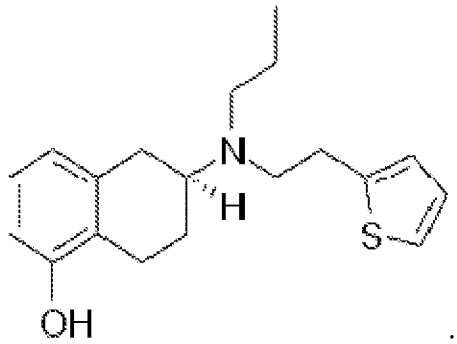
"In standard binding assays, rotigotine demonstrated the highest affinity for dopamine receptors, particularly the dopamine **D_3** receptor (K_i = 0.71 nM) **with its affinities to other dopamine receptors** being (K_i in nM) $D_{4.2}$ (3.9), $D_{4.7}$ (5.9), D_2 (13.5), $D_{4.4}$ (15), and D_1 (83)...In newly developed reporter-gene assays for determination of functional activity, rotigotine behaved as a full agonist at dopamine receptors (rank order: $D_3>D_{2L}>D_1=D_5>D_{4.4}$) with potenticies 2,600 and 53 times higher than dopamine at dopamine D_3 and D_{2L} receptors, respectively...Thus, in respect to PD, rotigotine can be characterized as a specific **dopamine receptor agonist with a preference for the D_3 receptor over D_2 and D_1 receptors**." *See* Scheller, *et al.* (2009) Naunyn-Schmiedeberg's Arch Pharmacol 379:73-86, at 73 (emphasis added, and submitted herewith). Therefore, Nichols' compounds and rotigotine do not share

the same D_2 agonist activity and thus the Office's rationale is in error and can not be used as a motivation to combine Nichols, Pfeiffer, and Lauterbach.

Furthermore, even if the receptor profiles were the same (which is not admitted herein), the compounds of Nichols are structurally different from rotigotine. Compare: Nichols' compounds represented by the following formula:



with rotigotine



.

There is no evidence of record to suggest one of ordinary skill in the art would be motivated to combine the cited art or that Nichols' compounds and rotigotine, which are so structurally and chemically different, could both effectively treat depression.

iii. Lauterbach and Pfeiffer Do Not Provide Any Motivation.

As acknowledged by the Examiner, Pfeiffer, at most, reports rotigotine in connection with Parkinson's disease. APO's failure to treat depression is evidence that a D_2 agonist effective to treat Parkinson's disease, is not necessarily able to treat depression just because of the drug's D_2 mechanism of action. Thus, Pfeiffer does not provide any motivation to combine Nichols and Lauterbach, or to treat depression. As set forth above, the Office Action concludes that "Lauterback teaches rotigotine in treating Parkinson's disease and further teaches that depression may also accompany Parkinson's disease." Lauterbach reports on the measured effects of rotigotine only on Parts II and III of the Unified Parkinson's Disease Rating Scale (UPDRS). Depression is only one aspect of behavior and mood included in Part I of the UPDRS. Treating a disease, such as Parkinson's disease, does not support the conclusion that the agent can also treat each symptom of the disease. Lauterbach does not teach that rotigotine has effective anti-depressive properties. Thus, similar to Pfeiffer,

Lauterbach does not provide any motivation to combine the cited documents.

Accordingly, the Office Action has failed to provide a motivation to combine the cited references and thus, fails to establish a presumption of *prima facie* obviousness.

3.2 No Predictability In Rotigotine Effectively Treating Depression

The Office Action (p. 7-8) also states that "since it is known that D2 agonist treat both depression and Parkinson's disease, one skilled in the art would be motivated to try a known effective D2 agonist that treats Parkinson's disease to also treat any type of depression or depression associated with Parkinson's disease." The "obvious to try" standard has been sanctioned by *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727, 82 USPQ2d 385, 396 (2007), but with the proviso that there has to be "a finite number of identified, predictable solutions" (emphasis added). Furthermore, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.*, emphasis added. As paraphrased in MPEP 2143.01.III (emphasis added), "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art."

i. The Entire Receptor Profile Is Needed to Determine Effectiveness In Treating Depression.

Effectiveness of a compound is not limited to its D_2 receptor profile. Effectiveness is based, in part, by the compound's complete receptor profile. As set forth in Scheller, *et al.* (2009) Naunyn-Schmiedeberg's Arch Pharmacol 379:73-86, at 73, "[t]o fully understand the pharmacological actions of rotigotine" or any compound, one must understand "its extended receptor profile." For example and as discussed above, Wang reports on the effects of APO, an agonist for the D_1 and D_2 receptors. Rather than just concluding that since APO is a D_2 agonist it would be effective, Wang studied the effect and APO failed.

Additionally, Bertaina-Anglade discusses the effectiveness of dopamine agonists in the treatment of depression and reports clinical trials for the D_2-D_3 receptor agonist, pramipexole. *See* Bertaina-Anglade, *et. al* (2006) European Journal of Pharmacology 548: 106-114 at pg. 107 (submitted herewith). However, Bertaina-Anglade still questions the efficacy of ropinerole, another D_2-D_3 receptor agonist, to treat depression. Accordingly, if one of ordinary skill in the art could predict efficacy from D_2 affinity, why would Wang and

Bertaina-Anglade be unable to predict the effectiveness of APO and ropinerole from pramipexole? The answer is one of ordinary skill could not predict such effectiveness just by simply knowing that rotigotine was a D_2 agonist – *i.e.*, the Office Action's rationale for reasonable expectation of success is contrary to the art of record.

Rotigotine's affinity profile actually further discourages an ordinary artisan to select rotigotine for depression treatment. Wang concludes that "the excessive stimulation of D_1 receptor may participate in the failure of coping behavior leading to learned helplessness and therefore in the pathophysiological mechanisms underlying the development of depression." As established above, rotigotine does have D_1 receptor activity. Therefore, the ordinary artisan would actually be discouraged from employing rotigotine for depression in light of Wang's teaching against D_1 receptor stimulation. Accordingly, the Office Action fails to provide sufficient evidence to establish that one of ordinary skill in the art, without knowledge of the full receptor profile, could predict effectiveness in rotigotine treating depression.

ii. There Is an Unreasonable Amount of Experimentation With No Guidance From Cited Art.

For the reasons discussed above, there is nothing within the cited documents that provide any guidance to arrive at the claimed invention. Knowing rotigotine is a D_2 agonist and effective at treating Parkinson's disease does not establish motivation or a reasonable expectation of success in treating depression with rotigotine. As set forth in Applicant's 8 March 2010 Request for Continued Examination this selection process, without any pattern of preference or guidance from the cited documents, would involve:

(1) Review of approximately 169 compounds that can act on dopamine receptors;
(2) Narrowing to approximately 128 compounds that are D_2 receptor acting compounds;
(3) Selecting approximately 30 compounds that are either D_2 agonists or partial agonists;
(4) Testing at least the 30 D_2 agonists or partial agonist compounds; and
(5) Finally, choosing 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol to treat depression.

Accordingly, without any guidance in the art, there is no pattern of preference for

choosing 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol or rotigotine, which has a completely different receptor profile from the Nichol's compounds. At best, the very large number of possible compounds (128 D_2 acting compounds, with at least 30 being D_2 agonists or partial agonists) provides only an invitation to "try" or "experiment" on the large number of agonists. It is apparent that in the instant case, "what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F. 2d 894, 903 (Fed. Cir. 1988). "In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009), emphasis added.

In conclusion, there is no reasonable expectation of success at least because:

- Rotigotine's full receptor profile was unknown;
- The documents of record teach that without the full receptor profile, the pharmacological effects were unpredictable;
- The documents of record conclusively establish that just because a compound is a D_2 agonist and used to treat Parkinson's disease, does not predict effectiveness in treating depression (*see,* for example, APO which failed);
- Rotigotine does not share the same D_2 activity as the Nichols' compounds, and in fact demonstrates mixed dopamine receptor activity, favoring the D_3 receptor; and
- The amount of experimentation is too great to provide any predictability or reasonable expectation of success. In order for an invention to be "obvious to try", there has to be a finite number of identified, predictable potential solutions to the recognized need or problem. MPEP §2143, citing *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 385 (2007).

Therefore, for at least these reasons a presumption of *prima facie* obviousness has not been established.

3.3 Conclusion: 3-way 35 USC §103(a) Rejection

Notwithstanding the Examiner's comments with regard to specific dependent claims, each of Claims 24-34, 37-55, and 78 is nonobvious over Nichols in view of Pfeiffer and Lauterbach for at least the same reasons that Claim 17 is nonobvious.

4. Rejection under 35 U.S.C. §103(a) over the Alleged 4-Way Combination of Nichols in view of Pfeiffer, Lauterbach and Maj

Claims 35 and 57 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 4 documents: Nichols in view of Pfeiffer and Lauterbach and further in view of U.S. Patent No. 6,255,329 (Maj). This 4-way rejection is respectfully traversed.

Claims 35 and 57 depend from Claim 17 and further include administering to a mammal an additional active ingredient, such as an antidepressant. For the reasons set forth above, a presumption of *prima facie* obviousness of Claim 17 (and thus of any claim dependent therefrom) over Nichols in view of Pfeiffer and Lauterbach is not sustainable. The addition of Maj to the previous 3-way combination of documents does not change this conclusion. Maj is cited for disclosure of a combination of pramipexole and sertraline. Thus, the fact remains that 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol was not known to effectively treat depression prior to the present invention.

Furthermore, the Examiner asserts that "[o]ne having ordinary skill in the art would have been motivated to use rotigotine for another drug (pramipexole) used in Parkinson's disease in combination with sertraline in treating depression because of expectation of therapeutic benefits, synergistic or additive effects." *See* Office Action at p. 10. At the time of invention, it was not possible to predict, in view of the cited art, the effectiveness of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol in treating depression, for the reasons discussed above, much less predict effectiveness of rotigotine in combination with an additional active ingredient, specifically an antidepressant.

In addition, to support this argument, the Office Action continues to rely on *In re Kerkhoven* as the motivation for combining the cited references. Applicant submits that the facts of this case are not comparable with those of *In re Kerkhoven*. For example, in *In re Kerkhoven*, the Court found that the claims at issue required no more than the mixing together of two conventional spray-dried detergents; thus, the claims were held to be *prima facie* obvious. In contrast to the spray-dried detergents of *In re Kerkhoven*, it cannot be said that

the combination of rotigotine with a second compound, such as an antidepressant, is "conventional" for treatment of depression. By failing to establish predictability in the claimed invention, the Office Action further fails to establish a presumption of *prima facie* obviousness of Claims 35 and 57.

Withdrawal of the present 4-way 35 U.S.C. §103(a) rejection of Claims 35 and 57 over Nichols in view of Pfeiffer and Lauterbach and further in view of Maj is respectfully requested.

5. Rejection under 35 U.S.C. §103(a) over the Alleged 5-Way Combination of Nichols in view of Pfeiffer, Lauterbach, Marquis and Timmerman

Claims 58 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 5 documents: Nichols in view of Pfeiffer and Lauterbach and further in view of U.S. Patent No. 6,350,773 (Marquis) and Timmerman *et al.* (1990) Eur. J. Pharmacol. 181:253–260 (Timmerman). This rejection is respectfully traversed.

Claim 58 depends from Claim 17, and includes administering to the mammal 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol and one of the specifically claimed antipsychotics. For the reasons set forth above, a presumption of *prima facie* obviousness of Claim 17 (and thus of any claim dependent therefrom) over Nichols in view of Pfeiffer and Lauterbach is not sustainable. The addition of Marquis to the previous 3-way combination of documents does not change this conclusion. Marquis is cited for disclosure of a D_2/D_3 agonist and an antipsychotic to treat depression. *See* Office Action, at p. 11-12. Similarly, the Office Action (p. 12) cites Timmerman as stating "N-0437 (rotigotine) [i]s an antipsychotic drug." However, Timmerman does not provide any motivation to treat depression with rotigotine, as it simply hypothesizes that "(+)N-0437 is a possible candidate for the therapeutic use in schizophrenia", and Timmerman does not discuss depression combination therapy with an antipsychotic. Thus, the fact remains that 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol was not known to have antidepressant activity prior to the present invention and the complete receptor profile of rotigotine was unknown, therefore the cited art fails to teach or suggest the invention as claimed in Claim 58.

Furthermore, the Examiner asserts that "[a] person of ordinary skill in the art at the

time of invention would have been motivated to use rotigotine (another D2 agonist) for another D2 agonist along with clozapine in treating depression in expectation of similar or better therapeutic benefits." *See* Office Action, p. 12. However, as discussed more fully above, rotigotine's effectiveness because it was a D_2 agonist or known to treat Parkinson's disease would not provide one of ordinary skill in the art with an expectation of success in treating depression. This is evidenced by, for example, other drug failures, like APO, which is a D_2 agonist used to treat Parkinson's disease. Thus, at the time of invention, it was not possible to predict, in view of the cited art, the effectiveness of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol much less in combination with an additional active ingredient, specifically an antipsychotic.

Withdrawal of the present 5-way 35 U.S.C. §103(a) rejection of Claim 58 over Nichols in view of Pfeiffer and Lauterbach and further in view of Marquis and Timmerman is respectfully requested.

6. Rejection under 35 U.S.C. §103(a) over the Alleged 5-Way Combination of Nichols in view of Pfeiffer, Lauterbach, Hrdlička, and Timmerman

Claims 58 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 5 documents: Nichols in view of Pfeiffer and Lauterbach and further in view of Timmerman and Hrdlička (2002) Eur. Psychiatry 17:484 (Hrdlička). This rejection is respectfully traversed.

As stated above, Claim 58 depends from Claim 17, and includes administering 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol and one of the specifically claimed antipsychotics. For the reasons set forth above, a presumption of *prima facie* obviousness of Claim 17 (and thus of any claim dependent therefrom) over Nichols in view of Pfeiffer and Lauterbach is not sustainable. The addition of Hrdlička to the previous 3-way combination of documents does not change this conclusion. Hrdlička is cited for disclosure of a one-patient study of a combination of clozapine and maprotiline. Thus, the fact remains that 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol was not known to have antidepressant activity prior to the present invention, therefore the cited art fails to teach or suggest the invention as claimed in Claim 58. Similarly, the Office Action (p. 13) cites Timmerman as stating "N-0437 (rotigotine) [i]s an antipsychotic drug." However,

Timmerman does not provide any motivation to treat depression with rotigotine, as it simply hypothesizes that "(+)N-0437 is a possible candidate for the therapeutic use in schizophrenia", and Timmerman does not discuss depression combination therapy with an antipsychotic.

Furthermore, the Examiner asserts that "[o]ne having ordinary skill in the art would have been motivated to administer one anti-psychotic drug (rotigotine) for clozapine in Hrdlicka's method of treating psychotic depression treatment in expectation of similar and or better therapeutic benefits of treating depression." *See* Office Action, p. 13. However, as discussed more fully above, because rotigotine is a D_2 agonist or known to treat Parkinson's disease does not provide an expectation of success in treating depression. This is evidenced by, for example, other drugs that were effective at treating Parkinson's disease and D_2 agonists and failed. Thus, at the time of invention, it was not possible to predict, in view of the cited art, the effectiveness of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol, much less in combination with an additional active ingredient, specifically an antipsychotic. By failing to establish predictability in the claimed invention, the Office Action further fails to establish a presumption of *prima facie* obviousness.

Withdrawal of the present 5-way 35 U.S.C. §103(a) rejection of Claim 58 over Nichols in view of Pfeiffer and Lauterbach and further in view of Hrdlička and Timmerman is respectfully requested.

7. Rejection under 35 U.S.C. §103(a) over the Alleged 4-Way Combination of Nichols in view of Pfeiffer, Lauterbach and Rimpler

Claim 60 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 4 documents: Nichols in view of Pfeiffer, Lauterbach and U.S. Patent Application No. 2003/0180332 (Rimpler). This rejection is respectfully traversed.

Claim 60 depends from Claim 17 and is drawn to a method of Claim 17 that further includes administering to the mammal one of the specifically claimed sedatives. For the reasons set forth above, a presumption of *prima facie* obviousness of Claim 17 (and thus of any claim dependent therefrom) over Nichols in view of Pfeiffer and Lauterbach is not sustainable. The addition of Rimpler to the combination of documents does not change this conclusion. Rimpler is cited for the disclosure of rotigotine in combination with

diphenhydramine. Rimpler does not teach or disclose employing rotigotine for the treatment of depression; thus, the fact remains that 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol was not known to have antidepressant activity prior to the present invention, therefore the cited art fails to teach or suggest the invention as claimed in Claim 60.

Withdrawal of the present 4-way 35 U.S.C. §103(a) rejection of Claim 60 over Nichols in view of Pfeiffer and Lauterbach and further in view of Rimpler is respectfully requested.

8. Rejection under 35 U.S.C. §103(a) over the Alleged 5-Way Combination of Nichols in view of Pfeiffer, Lauterbach, Kupfer, and Cook

Claim 60 also stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 5 documents: Nichols in view of Pfeiffer and Lauterbach and further in view of Kupfer (1999) Ann. Clin. Psychiatry 11:267–276 (Kupfer) and U.S. Patent Application Publication No. 2002/0177626 (Cook). This rejection is respectfully traversed.

Claim 60 depends from Claim 17 and is drawn to a method of Claim 17 that further includes administering to the mammal one of the specifically claimed sedatives. For the reasons set forth above, a presumption of *prima facie* obviousness of Claim 17 (and thus of any claim dependent therefrom) over Nichols in view of Pfeiffer and Lauterbach is not sustainable. The addition of Kupfer and/or Cook to the combination of documents does not change this conclusion. Kupfer is cited for the disclosure that "depressed patients often report problems sleeping and epidemiologic evidence suggests that insomnia may proceed the onset of depression." *See* Office Action, at p. 15. Cook is cited for disclosing diphenhydramine is a sedative. However, the fact remains that 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol was not known to have antidepressant activity prior to the present invention, much less in combination therapy with the claimed sedatives. Therefore the cited art fails to teach or suggest the invention as claimed in Claim 60.

Withdrawal of the present 5-way 35 U.S.C. §103(a) rejection of Claim 60 over Nichols in view of Pfeiffer and Lauterbach and further in view of Kupfer and Cook is respectfully requested.

9. Rejection under 35 U.S.C. §103(a) over the Alleged 5-Way Combination of Nichols in view of Pfeiffer, Lauterbach, Zimmerman, and Lehmann

Claim 62 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 5 documents: Nichols in view of Pfeiffer and Lauterbach and further in view of Zimmerman & Chelminski (2003) Am. J. Psychiatry 160:504–512 (Zimmerman) and Lehmann (1989) Neuropsychobiology 21:197–204 (Lehmann). This rejection is respectfully traversed.

Claim 62 depends from Claim 17 and is drawn to a method of Claim 17 that further includes administering to the mammal a specifically claimed anxiolytic. For the reasons set forth above, a presumption of *prima facie* obviousness of Claim 17 (and thus of any claim dependent therefrom) over Nichols in view of Pfeiffer and Lauterbach is not sustainable. The addition of Zimmerman and Lehmann to the combination of documents does not change this conclusion. Zimmerman is cited for the disclosure that depression can be accompanied by generalized anxiety disorder (GAD). Lehmann is cited for reporting that fluspirilene is an anxiolytic. Thus, the fact remains that 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol was not known to have antidepressant activity prior to the present invention. At the time of invention, it was not possible to predict, in view of the cited art, the effectiveness of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol, much less in combination with an additional active ingredient, specifically an anxiolytic. By failing to establish predictability in the claimed invention, the Office Action further fails to establish a presumption of *prima facie* obviousness.

Withdrawal of the present 5-way 35 U.S.C. §103(a) rejection of Claim 62 over Nichols in view of Pfeiffer and Lauterbach and further in view of Zimmerman and Lehmann is respectfully requested.

10. Rejection under 35 U.S.C. §103(a) over the Alleged 5-Way Combination of Nichols in view of Pfeiffer and Lauterbach, Medicine News, and Livingstone

Claim 64 stands rejected under 35 U.S.C. §103(a) as allegedly unpatentable over 5 documents: Nichols in view of Pfeiffer and Lauterbach and further in view of Anon. (2003) "Links between depression and migraine" www.bio-medicine.org/medicine-news/Links-between-Depression-and-Migraine-2005-1/ (Medicine News) and U.S. Patent Application Publication No. 2003/0225002 (Livingstone). This rejection is respectfully traversed.

Claim 64 depends from Claim 17 and is drawn to a method of Claim 17 that further includes administering to the mammal a specifically claimed anti-migraine agent. For the reasons set forth above, a presumption of *prima facie* obviousness of Claim 17 (and thus of any claim dependent therefrom) over Nichols in view of Pfeiffer and Lauterbach is not sustainable. The addition of Medicine News and Livingstone to the combination of documents do not change this conclusion. Medicine News is cited for the disclosure that treatments for migraine and major depression can benefit patients with both disorders. The Office Action cited Livingstone as disclosing that almotriptan is an anti-migraine agent. Thus, the fact remains that 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol was not known to have antidepressant activity prior to the present invention, therefore, the cited art fails to teach or suggest the invention as claimed in Claim 64.

Furthermore, the Examiner asserts that "[o]ne having ordinary skill in the art would have been motivated to use an anti-migraine agent along with an antidepressant in combination therapy in treating depressive patients to provide therapeutic benefits for migraine." *See* Office Action, at p. 17. However, at the time of invention, it was not possible to predict, in view of the cited art, the effectiveness of 5,6,7,8-tetrahydro-6-[propyl-[2-(2-thienyl)ethyl]amino]-1-naphthol, much less in combination with an additional active ingredient, specifically an anti-migraine agent. By failing to establish predictability in the claimed invention, the Office Action further fails to establish a presumption of *prima facie* obviousness.

Withdrawal of the present 5-way 35 U.S.C. §103(a) rejection of Claim 64 over Nichols in view of Pfeiffer and Lauterbach and further in view of Medicine News and Livingstone is respectfully requested.

11. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner

is invited to telephone the undersigned at the number below.

Respectfully submitted,

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/ Molly B. Edwards /

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